Demographic, Clinical and Genetic Features of the Patients with Familial Mediterranean Fever

Ailevi Akdeniz Ateşi Hastalarının Klinik, Demografik ve Genetik Özellikleri

Features of the Familial Mediterranean Fever

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Özet

Amaç: Bu çalışmaAilevi Akdeniz Ateşi (FMF) olan hastaların klinik, demografik ve genetik özelliklerini analiz etmeyi amaçlamaktadır. Gereç ve Yöntem: Bu çalışmaya FMF tanılı 150 hasta (96 erkek, 54 bayan) dahil edildi. Hastalar demografik özellikleri, klinik bulguları ve genotipik özellikleri bakımından istatistiksel olarak değerlendirildi. Bulgular: Çalışmaya dahil edilen 150 hastadan %64'ü (n=96) bayan , %36'sı (n=54) erkekti. Hastalar klinik özelliklerine göre incelendiğinde her iki cinste en sık gözlenen klinik bulgu karın ağrısıydı. Amiloidoz hastaların % 2'sinde (n=3) tespit edildi ve bunların tümü erkek hastaydı. Hastalarda tespit edilen en yaygın mutasyon M694V (n=153, %51) idi. En yaygın genotip M694V/M694V idi. FMF'li 7 hastanın (%4.6) mutasyon analizi negatif olarak bulundu. Mutasyonlarla klinik bulgular arasındaki ilişki incelendiğinde, homozigot M694V mutasyonlu hastalarda amiloidoz (p<0.001) ve karın ağrısı (p=0.04) sıklığı anlamlı olarak daha fazla bulundu. Hastaların %97.3'ü (n=146) kolşisin tedavisine cevap verdi. Tartışma: Bu çalışmada homozigot M694V mutasyonlu hastalarda amiloidoz ve karın ağrısı sıklığı anlamlı olarak daha fazla bulundu. Ayrıca FMF'in teşhisinde 9 yıllık önemli bir gecikme olduğu görüldü.

Anahtar Kelimeler

Ailevi Akdeniz Ateşi; Genotip-Fenotip İlişkisi; Amiloidoz; MEFV Gen Mutasyonu

Abstract

Aim: This study aims to analyze the demographic, clinical and genetic features ofthe patients with familial Mediterranean fever (FMF). Material and Method: A total of 150 patients (96 men and 54 women) with FMF were included to this study. Demographic characteristics, clinical findings, and genotypic features of the patients were statistically evaluated. Results: Percentages of male and female subjects were64% and36%, respectively. The most common clinical finding in both sexeswasabdominal pain. Amyloidosis was determined in 3patients (2%), and all of them were men. The most common mutation observed in thepatients was M694V (n=153, 51%). Mutation analyseswere negative in 7 (4.6%) patients. M694V/M694Vwas the most common genotype.In the patients with homozygous M694V mutation, amyloidosis (p<0.001) and abdominal pain (p=0.04) were the most frequently encountered clinical finding.Almost all of the patients (n=146, 97.3%) treated with colchicine. Discussion: In the present study, amyloidosis and abdominal pain were found to be significantly more frequent in patients with homozygous M694V mutation. There was, however, a significant delay of 9 yearsin diagnosis of FMF.

Keywords

Familial Mediterranean Fever; Genotype-Phenotype Relation; Amyloidosis; MEFV Gene Mutations

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive, autoimmune disorder characterized by recurrent bouts of fever and serosal inflammation [1].

FMF more frequently affects certain populations around the Mediterranean basin, which includes Sephardic Jewish, Armenian, Arabic, and Turkish societies [1]. Recent studies report that there are more than 100,000 patients diagnosed with FMF worldwide [1]. The rate of disease is reported to be 1/1073 in the Turkish population [2]. In Turkey, the disease is more common among people living in Central and Eastern Anatolia than those in the Mediterranean region [3]. In Central Anatolia this rate increases to 1/395 [4]. The carrier frequency is 1/5 in the Turkish population, 1/7 in Armenians, and 1/11 in Jews [5]. Although the disease is more common in societies around the Mediterranean basin, patients from different regions of the world have been diagnosed in recent years [6].

Etiopathogenesis of the disease is not clearly understood, but it is considered to be triggered by the proinflammatory process initiated by MEFV (Mediterranean fever) gene mutations. Approximately 100 or more disease-related mutations have been defined. The most common 5 mutations are M694V, M680I, M694I, E148Q, and V726A; they have been observed in 70% of the FMF cases [4]. Amyloidosis is the most important complication determining the prognosis of FMF [7].

Clinical findings may vary among different ethnic groups as well as among patients from the same ethnic origin who live in different geographical regions. For example, arthritis is seen more often in Turkish and Jewish subjects, while pleuritis is seen more often in Armenians [8]. It has been shown that the frequency of amyloidosis was higher in patients living in Armenia as compared to patients in the USA. Similarly, the frequency of amyloidosis is higher in Turkish subjects living in Turkey than those living in Germany. All these findings prove the combined effect of ethnic and environmental factors in the etiopathogenesis [9].

In this study, we aimed to evaluate the demographic and genetic characteristics and clinical findings of patients who applied to the Rheumatology and Nephrology outpatient clinics and were diagnosed as FMF according to the Livneh criteria [10]. We also emphasize the importance of early diagnosis.

Material and Method

This study includes 150 FMF patients (96 males and 54 females) who applied to the Rheumatology, Nephrology, and Internal Medicine departments of Atatürk Education and Research Hospital between August 2009 and August 2010. FMF diagnosis was based on the Livneh criteria [10]. The study protocol was approved by the local ethics committee in accordance with the Helsinki declaration of 2008.

The patients were divided into two groups according to the onset of symptoms. The patients whose symptoms started before and after the age of 20 were classified as 'early-onset FMF' and 'adult-onset FMF,' respectively.

Six different gene mutations were identified by gene mutation analyses. Homozygous and heterozygous forms of the 3 most common mutations were assessed statistically in terms of demographic and clinical characteristics.

Statistical Analysis

Data analysis was performed using the SPSS software package program (SPSS for Windows, version 16.0, SPSS Inc. Chicago, IL). Descriptive statistics for continuous variables were shown as mean, standard deviation, minimum and maximum values, and numbers and percentages of the observations.

In comparisons, Kolmogorov-Smirnov test was used to determine the distribution of the variables, and it was observed that they had a skewed distribution. As a result, Kruskal-Wallis and Mann-Whitney U tests were used for between-groups comparisons, and crosstab statistics (Chi-square and Fisher's Exact Test) were used for the comparisons of categorical variables. $p<0.05$ values were accepted as statistically significant.

Results

Demographic characteristics of the patients and the distribution of some variables are shown in Table 1.

Table 1. Demographic characteristics of patients

Mean age	35.48 ± 12.03(13-63)
Female	54 (36%)
Male	96 (64%)
Age of disease onset (years)	24.51 ± 10.55 (7-55)
Age of diagnosis (years)	33.13 ± 11.58(11-60)
Delay time of diagnosis (years)	9.39 ± 1.92 (1-20)
With family history	102 (68%)
Without family history	48 (32%)
Region of origin	
-Central Anatolia	128 (% 85,3)
-Eastern Anatolia	12 (% 8)
-Black Sea	9 (% 6)
-Mediterranean	1 (% 0,7)

In the assessment of the clinical features:

Abdominal pain was seen in 89 patients (59.34%), the most common clinical finding in both sexes. There was no significant difference between the male and female patients in terms of frequency of abdominal pain ($p> 0.05$).

Fifteen patients (10%) had recurrent fever that lasted for a minimum of 12 hours and a maximum of 10 days.

Fifteen patients (10%) had arthritis. Joint involvement was largely mono articular (n=82, 55.1%). Sixty-seven patients (44.9%) had multiple joint involvements. Ankle joints were the most affected joints (n=10, 66.6%), followed by knee (n=2, 13.3%), wrist (n=2, 13.3%), and hip (n=1, 6.8%) joints. The average duration of joint involvement was found to be 4.2 days. No sequelae were reported in these patients.

Chest pain was observed in 10 patients (6.67%). Eight patients (5.34%) had erysipelas-like erythema (ELE), which occurred concomitantly with arthritis or as a separate clinical finding during the monitoring of FMF patients. Joint involvement was also detected in four of them (2.6%). Eighty-nine patients (59.3%) had a prior history of appendectomy. One hundred and forty-six patients (97.3%) responded to treatment with colchicine. Of these, 66 (45.2%) had full responses and 80 (54.8%) had partial responses.

Other rare clinical findings, i.e., recurrent oral aphthae, low back

pain, and myalgia, were observed in 6 patients (4%). There was no significant difference between genders in terms of arthritis, chest pain, ELE, appendectomy, response to treatment, and the rare clinical findings (p>0.05) (Table 2).

Table 2.Clinical characteristics of patients

Characteristics	Number of patients	%
Abdominal pain	89	59.34
Fever	15	10
Arthritis	15	10
Chest pain	10	6.67
Erysipelas-like erythema	8	5.34
Other (recurrent oral aphthae, low back pain, arthralgia)	6	4
Amyloidosis	3	2
Appendectomy	89	59.3
Response to colchicine	146	97.3
No response to colchicine	4	2.7

Amyloidosis was determined in 3 patients (2%). All of the patients with amyloidosis were male. The frequency of amyloidosis was significantly higher in men than in women (p<0.05).
One hundred and twelve patients (74.6%) were identified as early-onset, 38 (24.6%) as adult-onset, and 1 (0.8%) as late-onset. Six different types of mutations and 15 different genotypes were identified in our study group of 150 FMF patients. The most common type of mutation was M694V with 51% (n=153), followed by M680I (18%, n=54), E148Q (7.3%, n=22), V726A (4%, n=12), P369S (1%, n= 3), and R653H (0.33%, n=1) (Table 3).

Table 3. Mutation types and distributions of patients with FMF

Mutationtype	Chromosome (n=300)	%
M694V	153	51
M680I	54	18
E148Q	22	7,3
V726A	12	4
P369S	3	1
R653H	1	0,33

These mutations were classified as homozygous, compound heterozygous, and heterozygous according to the forms present in the patients. Homozygous M694V was the most common genotype (n=57, 38%). The least common genotypes were homozygous V726A mutation (n=1, 0.6%), compound heterozygous M680I/V726A mutation (n=1, 0.6%), and compound heterozygous M680I/R653H mutation (n=1, 0.6%). Mutation analysis results of 7 patients with FMF (4.6%) were found to be negative (Table 4).
Amyloidosis and abdominal pain were found to be more frequent in patients with homozygous M694V mutation at a statistically significant level (p<0.001 and p=0.04, respectively).

Table 4. Genotypiccharacteristicsanddistributions in patientswith FMF

Mutationtype	Number of patients	%
Homozygous		
-M694V/M694V	57	38
-M680I/M680I	21	14
-E148Q/E148Q	8	5,3
-V726A/V726A	1	0,6
Compound heterozygous		
-M694V/E148Q	7	4,6
-M694V/V726A	6	4
-M694V/M680I	4	2,6
-E148Q/P369S	3	2
-M680I/V726A	1	0,6
-M680I/R653H	1	0,6
Heterozygous		
-M694V/-	22	14,6
-M680I/-	6	4
-V726A/-	3	2
-E148Q/-	3	2
Negative	7	4,6

Discussion

This study demonstrated that there is still a delay in the diagnosis of FMF in spite of the development of diagnostic tools such as genetic testing. In the present study, the delay in diagnosis was as long as nine years.
FMF is thought to affect both genders equally. In a study carried out by the Turkish FMF Study Group in a patient population comprising both adults and children, the male-female ratio for the incidence of FMF was found to be 1.2/1 [11]. Duşunsel et al. [12] determined the male-female ratio to be 1/1.3 and stated that this result was not statistically significant. In the present study, this ratio was found to be 1.7/1.
The overall incidence of FMF is reported to be 0.1% in Turkey, but the rate is as high as 1/395 in the central Anatolia region. A recent study carried out in Tokat province reported this incidence as 1/123 [13]. A majority of FMF patients in Turkey are originated from regions away from the Mediterranean region. Patients are more often from the Central Anatolia, Black Sea, and Eastern Anatolia regions. According to a study by Ureten et al. [14] in FMF patients, 68.3%, 20%, and 8.3% of the patients originate from the Central Anatolia, Black Sea, and Eastern Anatolia regions, respectively. In the present study, however, 85.3% (n=128), 8% (n=12), 6% (n=6), and 0.7% (n=1) of the patients originate from the Central Anatolia, Eastern Anatolia, Black Sea, and Mediterranean regions, respectively. This can be explained by the fact that the regions mentioned above are geographic locations where consanguineous marriage is most commonly seen. The high rate of positive family history in FMF patients (68%) also supports this view. The rate of consanguineous marriage in Turkey is found to be 27% [15].
According to the reports of the Turkish FMF Study Group, the average delay time of diagnosis in Turkey is 6.9 years [11]. Ureten et al. [14] reported that the average delay time was 9.39 years and the rate of appendectomy 20%. In the present study, average delay time was found to be 9.39 ± 8.9 years and the appendectomy rate was 59.3%.
In a study carried out by Sayarlıoğlu et al. [16] in 401 FMF patients, 57 patients (14%) were determined to have adult-onset FMF versus only 5 patients (1.25%) with late-onset FMF. Ureten

et al. [14] carried out a study of 260 FMF patients and identified 77 of them (30%) as adult-onset FMF patients. There was no late-onset FMF case in their study group. In the present study, 112 (74.6%) of the 150 patients had early-onset FMF, 37 subjects (24.6%) adult-onset FMF, and 1 subject (0.8%) late-onset FMF.

In the study of Sayarlıoğlu et al. [16] the average delay time of diagnosis was 12.1 years in early-onset patients, while it was 6 years in adult-onset patients. In terms of clinical findings, arthritis and ELE were significantly less common in adult-onset cases. In the study of Ureten et al. [14], the average delay time of diagnosis was found to be 10.31 and 7.25 years in early-onset and adult-onset cases, respectively. Arthritis and ELE were the most common clinical findings in early-onset cases. Similar results were also reached in the study carried out by Saatci et al. [17]. According to their results, the delay time of diagnosis was longer in early-onset patients, and arthritis and ELE were the most common clinical findings in early-onset cases [17]. In the present study, the average delay time of diagnosis was found to be 10.23 ± 10.17 years in early-onset cases and 7.37 ± 7.33 years in adult-onset cases. The reason for the longer delay time of diagnosis in early-onset cases could be the common childhood diseases such as infections or acute rheumatic fever that are generally taken into consideration in differential diagnosis.

The most common clinical findings in our study were abdominal pain (40%), ELE (29.4%), and arthritis (20.5%) in early-onset cases, but abdominal pain (36.8%) and fever (36.8%) in adult-onset cases. Arthritis was the least common clinical symptom in adult-onset cases (5.2%). In a study carried out by Gürkan et al., early- and adult-onset cases were compared in terms of the annual number of attacks, the disease severity score, and the development of amyloidosis, and it was found that early-onset cases had a higher number of annual attacks and higher severity scores. In this study, all patients developing amyloidosis were adult-onset cases [18]; this result was similar to our finding.

It has been suggested that the most common clinical findings of FMF patients are abdominal pain in Arabic [19] and Turkish [14] patients, but abdominal pain and arthritis in Jewish patients [20]. In the present study, abdominal pain was the most frequent clinical finding in FMF patients, with a rate of 59.4%. Abdominal pain was followed by fever and arthritis. Arthritis was the only symptom occurring during the onset of the disease in four FMF patients (2.6%). Ozalkaya et al. [5] stated that joint-related findings could be the most frequently encountered symptom, particularly during the childhood period.

The most feared complication of FMF is amyloidosis. In the present study, amyloidosis was seen in three patients, all of them male. Moskovitz et al. [21] compared the clinical and demographic characteristics of male and female patients and found no statistically significant difference regarding amyloidosis development. Onen et al. [1] reported that males had a possible risk factor in the development of amyloidosis. Various studies have indicated that genotypic characteristics play a major role in both the frequency of clinical symptoms and in amyloidosis development.

The most common MEFV gene mutations identified in Turkish FMF patients are M694V, M680I, V726A, and E148Q. According to the study carried out by Yilmaz et al. [4], M694V was the most common mutation (43.5%) in Turkish FMF patients. In the present study, 143 (95.3%) of the 150 patients had MEFV gene mutation. No gene mutation was seen in 7 patients (4.7%). Kaşifoğlu et al. [22] showed that homozygosity for M694V confers a 6-fold higher risk of amyloidosis than the other mutations. Altunoğlu et al. [23] emphasized that amyloidosis could develop in FMF patients with no M694V mutation. In the present study, amyloidosis and abdominal pain were found to be significantly more frequent in patients with homozygous M694V mutation. All these data indicate that every patient diagnosed as FMF should receive treatment for amyloidosis development even if homozygous M694V mutation is absent [24].

Many studies regarding the frequencies of FMF mutations have shown that E148Q was less frequent than the other mutations [8]. In our study, however, E148Q was the third most frequently seen mutation with a percentage of 7.3% (n=22). According to Booth et al. [25], it was the second most frequent mutation. Lower frequencies of E148Q mutations in other studies can be explained by low penetration of the mutation due to its localization on the MEFV gene. Low phenotypic penetration sometimes makes individuals with heterozygous or even homozygous E148Q mutation asymptomatic for FMF and causes low frequency of detection in mutation screenings of FMF patients [30]. Further community screenings in ethnic groups where FMF is common can help to identify the real incidence of E148Q.

As a conclusion, this study revealed that the most common MEFV gene mutation was M694V. Genotype-phenotype correlation analysis showed that the homozygous forms of these mutations led to a significant increase in amyloidosis development. It was also shown that consanguineous marriages often seen in Turkey increase the risk of bringing together mutant alleles of this disease having a high carrier frequency. Also, FMF signs often could be mistaken for appendicitis. Therefore, far-reaching community screenings are required to identify carriers and appropriate genetic consultancy services should be provided for these individuals.

The limitations of our study included missing patient file information which made it impossible to calculate disease severity scores. Strengths of the study include the high number of cases and the detailed description of the genotype-phenotype correlation.

Competing interests

The authors declare that they have no competing interests.

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